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T cell immunity to commensal fungi

Alexander Scheffold[1], Petra Bacher[1,2] and Salomé LeibundGut-Landmann[3,4]

Fungi are an important part of the microbiota in healthy barrier tissues. Fungal dysbiosis in turn is associated with local and distal inflammatory diseases. Recent advances have shed light on the antigen-specific IL-17-dependent mechanisms that regulate fungal commensalism and prevent fungal overgrowth during homeostasis. Progress in our understanding of species-specific differences in fungus-host interactions provides new hypotheses of why *Candida albicans*-targeting T cells exceed those directed against other fungal species in the human T cell repertoire. Importantly, *C. albicans*-specific Th17 cells can also contribute to immune pathology in distant organs such as the lung via cross-reaction with heterologous antigens.

Addresses
[1] Institute of Immunology, Christian-Albrechts Universität zu Kiel and Universitätsklinik Schleswig-Holstein, Kiel, Germany

[2] Institute of Clinical Molecular Biology, Christian-Albrechts Universität zu Kiel, Kiel, Germany
[3] Section of Immunology, Vetsuisse Faculty, University of Zürich, Switzerland
[4] Institute of Experimental Immunology, University of Zürich, Switzerland

Corresponding author:
LeibundGut-Landmann, Salomé (salome.leibundgut-landmann@uzh.ch)

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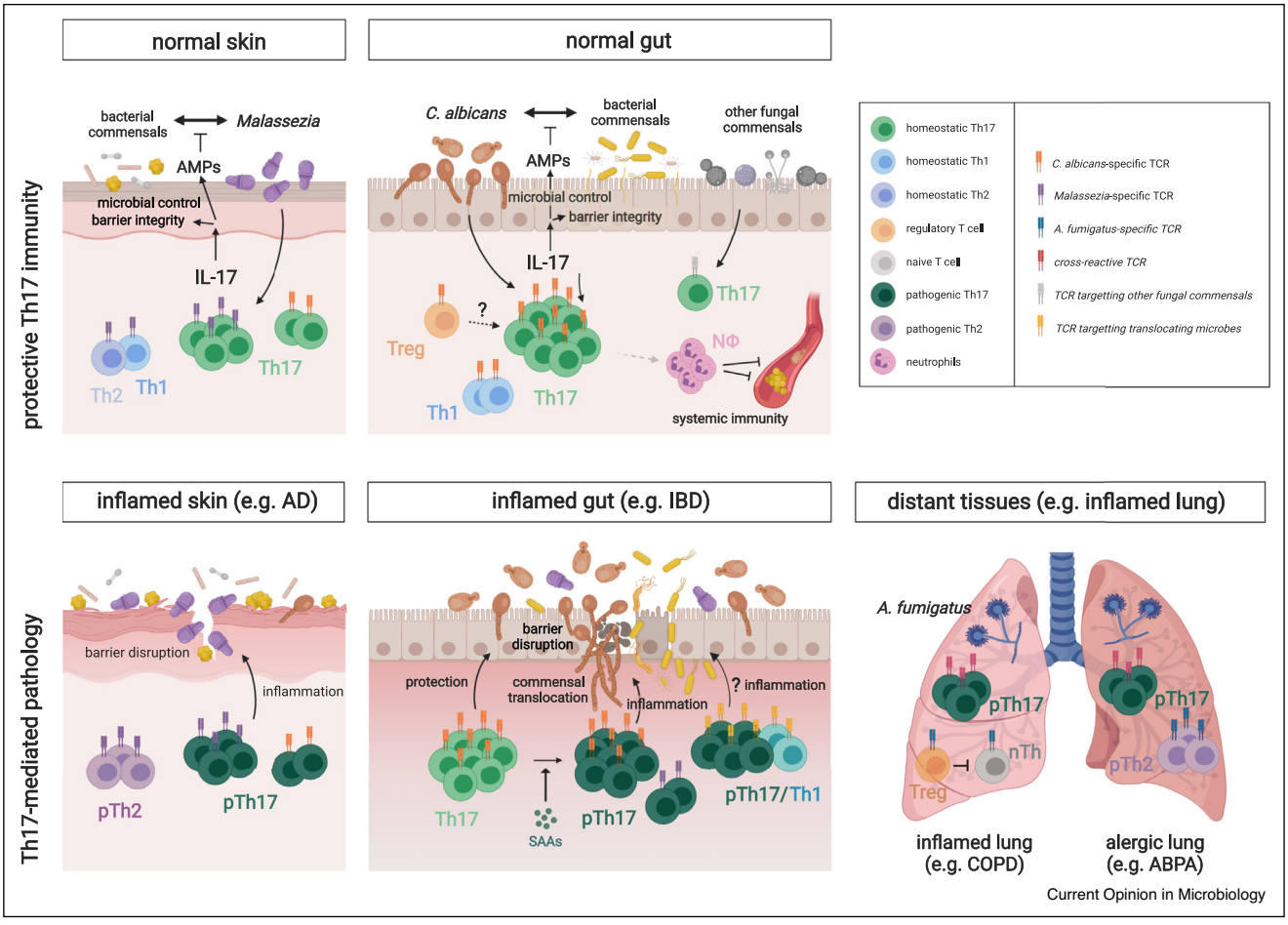
Introduction

The microbiota forms an essential component of human body homeostasis and the direct microbiota-host interaction at barrier tissues is a central regulatory knot affecting many human diseases. Fungi are an integral, though largely neglected part of the microbiota [1]. However, recent data highlight certain fungal species as prototypic examples for microbiota-mediated immune modulation in humans. Fungi interact with the immune system via molecular patterns triggering innate immune receptors. However, due to sharing of those molecular patterns between fungi, the contribution of individual species to the overall antifungal response is not clear. Some commensal fungi, including *Aspergillus fumigatus*, *Candida albicans* and *Malassezia* spp. are potent inducers of antigen-specific T cell responses, equally or even exceeding that of bacterial or viral species [2••]. Thus, they represent prototypic examples to define the principles of homeostatic immunity and how T cell responses against commensals may impact on immune pathologies. Here we focus on *C. albicans* and *Malassezia* spp. as commensals of skin and mucosal tissues. The T cell response against *Aspergillus* spp. as representative of chronically encountered environmental fungi in the lung is summarized in Ref. [3]. Here we discuss recent advances in our understanding how fungal commensalism is regulated by T helper cells and how normally host-protective mechanisms directed against commensal fungi can drive pathology and disease. We alsohighlight open questions and challenges in the field.

Th17 mediated immunosurveillance of the mycobiota at epithelial barriers

Constant exposure to commensal microbes results in a continuous or repeated activation of the immune system at barrier tissues but obviously at a subclinical level. Active immune surveillance of the microbiota is critical to prevent dysbiosis, microbial overgrowth and translocation across epithelial barriers. Besides essential innate immune mechanisms, an active role for immune surveillance at barrier sites has especially been demonstrated for Th17 cells, and several Th17 inducing microbes have been identified in mice [4–6] including *C. albicans* and *Malassezia* spp. [7,8••,9] (Figure 1). Interestingly, human patients with genetic Th17 deficiencies suffer mainly from mucocutaneous candidiasis [10] in contrast to broader fungal susceptibilities of patients with innate immune defects [11]. Consistently, *C. albicans* is a major target of human Th17 responses [12,13]. Human Th17 responses also target other fungal species, especially *Malassezia* spp. [2••,8••] and IL-17A blockade was linked to *Malassezia*-associated pathology [14]. Anti-fungal T cells develop into tissue-resident memory T (T_{RM}) cells [15•,16•] to locally shield epithelial barriers while high frequencies commensal fungi-targeting memory T cells also circulate in the blood [2••,12]. *C. albicans* also induces specific $Foxp3^+$ regulatory T cell responses but numerically less than T effector cells [17,18]. Tregs may support Th17 development by IL-2 deprivation [19], although in a model for *C. albicans* commensalism, the depletion of Tregs did not interfere with homeostatic Th17 immunity or fungal colonization [20]. Thus, the functional role of Tregs for the antigen-specific homeostatic balance is not clear.

Figure 1



Protective and pathological effects of commensal fungi-specific Th17 cells in the skin, the gut and the lung.
Top row: T helper cells provide antigen-specific protection against fungal commensals in the normal skin and gut. The dominance of Th17 cells (green cells) directed against *C. albicans* (orange TCR) followed by Th17 cells directed against *Malassezia* (purple TCR) or any other commensal fungi (grey TCR) in the human T cell repertoire is indicated by the number of plotted cells. A small proportion of fungus-specific Th1 and Th2 cells (blue cells) can also be detected in humans. How Tregs modulate the Th17 response remains unclear (as indicated by a dotted arrow). IL-17 production in response to commensal fungi may regulate epithelial barrier integrity and/or antimicrobial peptide (AMP) production to promote microbial homeostasis including the equilibrium between bacterial and fungal commensals. *C. albicans*-specific Th17 cells may modulate neutrophil-mediated immunity against systemic infection with *S. aureus*. Bottom row: Predisposing conditions of the host, such as inflammation and epithelial barrier disruption of the skin (atopic dermatitis (AD)) or the gut (inflammatory bowel disease, IBD), which are characterized by microbial translocation, are associated with pathological effects of commensal fungi-specific Th17 cells (dark green cells), and Th2 cells (in case of AD, purple cells). Serum amyloid A (SAA) is one factor proposed to regulate the functional plasticity of Th17 cells in the gut. Commensal translocation may furthermore lead to the activation of Th17/Th1 cells that target translocated microbes and further exacerbate inflammation (yellow TCR) via a hitherto unclear mode of action. Th17 cells primed against *C. albicans* may also act in distant tissues and cross-react against other microbes, such as *A. fumigatus* in the inflamed lung (red TCR) to drive lung pathology (as in COPD, left side of the lung) or synergize with *A. fumigatus*-specific non-cross-reactive Th2 cells in the allergic lung during ABPA (right side of the lung).

Overall, only few microbial species, and in humans especially *C. albicans* induce strong Th17 responses indicative of firm but balanced interactions with the immune system and specialized properties to induce antigen-specific Th17 immunity. Further, *C. albicans* may broadly modulate Th17 responses against other fungi via cross-reactivity to shared fungal epitopes ([2••] and see below). Th17 cells have also been subdivided into 'pathogenic' versus 'non-pathogenic' Th17 cells, relating to their differential function in human diseases [21], but their *in vivo* relevance and potential induction pathways are unclear (see Box 1). Therefore, it will be of major importance to define the signals of Th17 cell differentiation, functional plasticity and maintenance in relation to antigen-specificity, *in vivo* priming conditions and the local tissue environment.

Box 1 Pathogenic Th17 cells: a matter of phenotype, location or both.

T helper cell subsets display a certain degree of plasticity. The plasticity concept integrates the possibility that certain lineages can adapt to environmental signals and gradually shut down lineage-specific features and instead co-express features of other lineages [74]. Plasticity is particularly evident for Th17 and Treg cells. The concept of ' pathogenic' and 'non-pathogenic' Th17 cells is largely based on *in vitro* Th17 induction protocols using different cytokine combinations, that is, IL-6, IL-1β and IL-23 versus IL-6 and TGF-β, respectively, and their capacity to induce disease in murine models [75]. Th17 cells can integrate different environmental signals and adapt functionality, as recently described for serum amyloid proteins promoting pathogenic Th17 cells locally in tissues during colitis and EAE [76••]. Th17 plasticity may also comprise acquisition of protective functions, as recently described for commensal-specific Th17 cells in murine skin [77•]. However, to which extent antigen-specific Th17 cells in humans are subjected to such plasticity is not clear. Interestingly, the prototypic Th17 cells targeting *C. albicans* and *S. aureus* phenotypically represent 'pathogenic' and 'non-pathogenic' Th17 subsets, respectively [78,79], despite the fact that both microbes do not normally cause pathology. It is also not clear if the *C. albicans*-specific fraction of Th17 cells cross-reactive to *A. fumigatus* in human lung may be pathogenic due to functional alterations or simply due to location and target specificity, that is, lung versus intestine or skin [2••]. Further work is required to determine how antigen-specificity, tissue site and environmental cues including inflammatory signals shape human Th17 functional plasticity [80].

Contribution of commensal fungi-specific memory T cells to immune protection and pathology

The microbiota has a broad beneficial or adverse impact on human health, but the contribution of fungal species is currently underappreciated. However, intestinal fungi, similarly to bacterial microbes, can modulate the intestinal balance [22] as well as the response to infections [22,23••] or allergy against distal heterologous antigens [24–26] with an important contribution of *C. albicans* in both, humans [27] and murine models [23••,28,29] (Figure 1). *C. albicans* or *Malassezia* overgrowth is also associated with human IBD [26,30] and exacerbated experimental colitis [30,31] and it may contribute to inflammation in patients with alcoholic liver disease [32,33•]. Increased *Candida* colonization in allogeneic hematopoietic stem cell transplant patients correlates with the incidence of invasive candidiasis [34••] and severe GvHD [35,36]. On the contrary, reduction of *Candida* colonization by faecal microbiota transplantation in ulcerative colitis patients correlates with a better disease outcome [37]. A role of *Malassezia* spp. in skin [8••] and lung [38] inflammation as well in carcinogenesis [39,40] has been described.

Thus, fungi broadly modulate local as well as systemic immune responses. However, the reported effects of commensals are not antigen-specific or species-specific. Most identified mechanisms so far include microbial 'patterns' including innate immune receptor ligands or metabolites. Thus, it is currently an open question how microbiota may modulate T cell-dependent, that is antigen-specific effects. Acute gastrointestinal infections can broadly modulate T cell reactivity against commensal microbes [41]. However, the non-acute or 'homeostatic' response to commensals is dominated by antigen-specific Th17 cells [2••,12,23••,42]. Thus, we will here focus on those few fungi known to leave a specific footprint within the T cell repertoire during host-microbiome interaction. We discuss how specific antigen recognition may contribute to local or distal immune protection or pathology, involving different types of target antigens and divers T cell functionalities.

Local effect of commensal fungi on T cell mediated immune homeostasis and inflammation

The strongest Th17 response in healthy humans known so far is directed against *C. albicans* [2••,12,17]. *Candida*-specific Th17 cells seem to be non-pathogenic but essential to prevent *C. albicans* overgrowth without causing overt inflammation (see Box 1). In murine colonization models, intestinal [23••] and oral [20] *C. albicans* induce a non-inflammatory fungus-specific Th17 response. Intestinal inflammation and damage may enhance antigen accessibility since *C. albicans*-specific Th17 responses are increased in the blood of IBD patients [2••] and their frequencies correlated with the fecal abundance of *C. albicans* in intensive care unit patients [23••]. However, IL-17 blockade in IBD patients has been proven ineffective or even harmful, suggesting that Th17 responses against *Candida* are not diseases-promoting, but rather protective in the inflamed gut, presumably via strengthening barrier repair functions. Thus the positive association between the intestinal abundance of *Candida* or *Malassezia* [30,31] and more severe IBD may, therefore, not primarily be mediated via IL-17, but via IL-17-independent mechanisms. Whether fungus-specific T cells contribute to IBD via acquisition of 'pathogenic' functions remains to be analyzed.

In the skin, *Malassezia* colonization induces Th17 cells which control fungal growth in mice [8••] but enhance the inflammatory responses upon epithelial damage in an IL-23 and IL-17-dependent manner [8••]. Similarly, in patients with atopic dermatitis increased Th17 responses against *Malassezia* were observed [8••,43]. *Malassezia*-reactive T cells may contribute to AD pathogenesis via cross-reactivity against conserved host proteins such as thioredoxin and manganese-dependent superoxide dismutase [43,44]. The relevance of IL-17 in disease pathogenesis of AD is not clear but may be most relevant in subtypes of the disease [45–47].

In psoriasis, the Th17 pathway plays a central pathogenic role. Although the antigens stimulating local IL-17 release are not identified so far, members of the skin microbiota or mycobiota are prime suspects. There are

variable reports on the composition of the microbiome and mycobiome in psoriatic skin [48] with *Malassezia* and *Staphylococcus* among the most frequent genera. Whether specific T cell and Th17 reactivity against these microbes are altered and causatively linked to disease in humans remains unclear [48]. In support of this idea, re-activation of commensal-specific Th17 cells can aggravate tissue inflammation in an experimental model of psoriasis [49•]. Moreover, the increased incidence of *C. albicans* infections in psoriasis patients treated with IL-17-targetting antibodies [50,51] indicates that interfering with the IL-17 response can modulate the mycobiota.

Systemic effects of commensal fungi on immune homeostasis and inflammation

Although it is known that the intestinal microbiota including the mycobiota affect immune responses at a distance, very little is known how fungus-specific T cells contribute to this process. *C. albicans* Th17 cells protect against systemic infection with unrelated pathogens and exacerbate lung allergy presumably via IL-17-mediated systemic neutrophil activation [23••]. This may involve T cell receptor-independent bystander activation [52,53]. However, it is becoming increasingly clear that cross-reactivity to commensal fungi affects systemic immune responses (see Box 2). Surprisingly, the majority of human fungus-specific Th17 cells, were shown to be cross-reactive against *C. albicans*, most likely via recognition of homologous epitopes [2••]. This suggests that human anti-fungal Th17 responses rely on cross-reactivity against *C. albicans* as a major direct Th17 inducer. Overall increased target diversity may broaden the Th17 protective function but may also enhance pathology. Indeed, cross-reactive Th17 cells reacting against *Aspergillus* expand and are recruited to the lung of patients with allergic bronchopulmonary aspergillosis [2••]. Importantly, these cross-reactive Th17 cells were not obviously functionally distinct from non-cross-reactive Th17 cells, suggesting that the decision between pathogenic and non-pathogenic may depend on the local tissue environment and the target antigen.

Box 2 Microbiota and TCR cross-reactivity in the human immune system.

Cross-reactivity, that is, recognition of two peptides, related or unrelated, by the same TCR, is often regarded as a rare phenomenon in immunology. However, its impact, mainly on virus-specific $CD8^+$ T cells has been well documented [81]. In fact, TCRs need to cross-react for providing comprehensive immune coverage and they indeed recognize multiple and even unrelated epitopes [82,83]. Humans also accumulate a highly divers memory TCR repertoire since they encounter many different antigens throughout life. Thus, neo-antigens can be recognized by memory as well as naïve T cells [13,84–86]. Other examples include microbe-specific memory T cells with cross-reactivity against other microbes [87], autoantigens [88] or allergens [81]. Furthermore, T cells involved in lung autoimmunity were found to express dual TCRs recognizing an intestinal commensal and an autoantigen, respectively [89]. We are only beginning to understand the diverse consequences of such cross-reactive T cells on antigen-specific immunity in infections, vaccination, autoimmune disease or allergies [81,83,88]. The commensal microbiota represents an enormous source of antigens, it can be expected to engage a significant fraction of the human T cell repertoire [90] and shape antigen-specific immunity. The broad modulation of human anti-fungal Th17 responses by the commensal fungus *C. albicans* discussed herein [2••] seems to be a particularly relevant example. However, cross-reactivity to microbiota in general provides a rational antigen-specific immune modulation by the microbiota. Therefore, it will be of utmost importance to resolve human immune protection and pathology on the level of antigen-specificity and to correlate specificity and potential cross-reactivity with functional activity, that is, protection versus pathogenicity.

Mechanistic aspects of commensal fungi-specific T cell immunity

C. albicans-reactive T cells in humans exceed those directed against other commensal or environmental fungi [2••] but the underlying cause remains unclear. Possible factors include differences in Th17-inducing PAMP exposure, in the expression of immune dominant and/or cross-reactive antigens and in tissue invasiveness, as we will discuss in the following section.

The Th17 polarizing cytokines IL-6, IL-1 and IL-23, are induced efficiently by fungal cell wall carbohydrates via Dectin-1, Dectin-2 or Mincle triggering the Syk/Card9 pathway [54]. The ligands are highly conserved across fungi but their exposure varies significantly due to variability in the cell wall architecture of different fungal species [55], which may be further modulated by environmental factors [56]. Taking into account this, *C. albicans* can be predicted to be among the strong inducers. However, experimental infection models demonstrate a strong Th17 inducing capacity of many other fungi, including *Malassezia* spp. [8••], *Aspergillus* [57], dermatophytes [58] and the dimorphic fungi [59]. Thus, innate receptor activation alone unlikely explains the superior Th17 inducing capacity of *C. albicans* in humans.

An alternative explanation for the prevalence of *C. albicans*-specific Th17 cells may be the availability of *C. albicans*-derived antigens early in life and/or specific characteristics of the antigens. *C. albicans* is found in the gastrointestinal tract shortly after birth [60] and also on the skin of children [61] and neonatal T cells efficiently respond to *C. albicans* [62]. In contrast, *Malassezia* reaches broad colonization of the skin only during puberty [63]. An early pool of *C. albicans*-specific Th17 cells may provide a source for recruitment of cross-reacting Th17 cells against other species and at the same time preventing *de novo* Th17 induction by other antigens. So far, only a small number of naturally processed and presented *C. albicans*-derived T cell antigens have been identified, some of which are conserved between even distantly related fungi [2••,64]. The recognition of shared epitopes provides an explanation for the cross-reactivity of *C.*

albicans-induced T cells [2••], although it remains to be proven whether cross-reactivity is indeed mediated antigen-specifically. Identifying the targeted epitopes, especially those targeted by Th17 cells, will be a key step in the future. It will also be interesting to determine whether T cells primed by fungi other than *C. albicans* can also exert cross-reactivity, and thus whether this represents a more general principle. Overall, mounting cross-reactive T cell populations against distinct microbial species may allow saving resources by sharing reactivity, which represents an advantage for the host but entail a risk for pathological consequences.

Adherence to the epithelia has been demonstrated to be a critical feature of murine Th17-inducing microbes, including *C. albicans* [6]. The potential of *C. albicans* to firmly interact with and invade epithelia exceeds that of other fungal commensals. Tissue damage by *C. albicans* triggers inflammation and epithelial invasion via the recently identified peptide toxin candidalysin, which promotes epithelial damage [65], epithelial translocation [66] and the release of Th17-triggering cytokines [67•,68•]. This has mainly been demonstrated by *in vitro* cultures and experimental models of acute primary infection characterized by inflammation and IL-17 production by innate lymphocytes [69,70]. Importantly, however, antigen-specific Th17 immunity is induced upon *C. albicans* colonization in the absence of inflammation and independently of strain virulence [71]. Also, all humans mount a *C. albicans*-specific Th17 cell response [2••,12] irrespective of the colonizing fungal strain. Thus, *C. albicans* colonization may provide a Th17 trigger without overt inflammation, thereby enabling peaceful coexistence. Interestingly *C. albicans* maintains its virulence only during co-colonization with bacterial microbiota suggesting an evolutionary benefit [72•]. Thus, it might be speculated that low-level invasion and Th17 induction provides a positive feedback loop creating a niche for *C. albicans* survival in a competitive intestinal environment. It will be important to set up suitable mouse models mimicking the chronic exposure to commensal fungi to decipher the relevant molecular details of Th17 induction.

Concluding remarks and future challenges

Immune protection and immune mediated diseases are highly antigen-specific processes, and it is a major gap in our understanding how microbiota modulates functionally diverse antigen-specific T cell responses contributing to health and disease. Commensal fungi play a pivotal but so far understudied role in this process. Despite their low abundance within the microbiota, fungi have emerged as potent inducers of antigen-specific T cell in humans, controlling homeostatic host-fungus interactions and contributing to immune pathology if dysregulated, as discussed herein for Th17 cells. These studies also highlight that cross-reactivity to microbiota is common within human T cell immunity and represents a neglected aspect of immune modulation, which has to be addressed in the future. However, there remain several open questions: Which members of the mycobiota or microbiota actively induce adaptive human immune responses and what regulates the balance between antigen-specific effector and regulatory T cell subsets? What defines phenotypic and functional features of protective and pathogenic Th17 cells, including the relation between tissue-resident and circulating T cells: antigen-specificity or tissue context? Comprehensive answers to these questions will depend on a combination of studies in humans and closely adapted model systems. Choosing relevant human-like models to adequately mirror homeostatic fungus-host interactions is critical with respect to fungal strain [71], complexity of the host microbiota [73•], duration and intensity of exposure, and antigen-specificity of the readouts.

Conflict of interest statement

Nothing declared.

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